



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Myopericarditis after COVID-19 vaccination: unexpected but not unprecedented



In the midst of the devastating COVID-19 pandemic, rapid development of highly effective vaccines was enthusiastically welcomed. Unfortunately, myopericarditis after COVID-19 vaccination was an unanticipated adverse event. In *The Lancet Respiratory Medicine*, Ryan Ruiyang Ling and colleagues commendably review the risk of this adverse event in the context of risk after other vaccines.¹ Their study provides an important perspective on the historical global experience with cardiac adverse events after vaccination.

Ling and colleagues applied rigorous statistical analyses to the available literature and confirmed the conclusions of other reviewers. Specifically, the overall incidence of myopericarditis after COVID-19 vaccination (18.2 cases [95% CI 10.9–30.3] per million doses) is not higher than expected outside of the context of vaccination, and not significantly higher than the incidence of myopericarditis reported after the standard immunisations included in the study, such as influenza vaccines (1.3 [0.0–884.1], $p=0.43$ vs COVID-19 vaccines). There is, however, an important demographic and vaccine-related component to this adverse event that is obscured in reporting the overall incidence. The risk of myopericarditis in young males after their second dose of mRNA COVID-19 vaccine is remarkably higher than expected.

This pattern has been seen before. As Ling and colleagues found when they reviewed the extant literature, myopericarditis risk is well established after receipt of live-replicating smallpox vaccine. Notably, in a study by Oster and colleagues² of myocarditis after mRNA COVID-19 vaccination, the rate of myocarditis reported in the highest-risk group of recipients (105.86 cases [95% CI 91.65–122.27] per million doses in males aged 16–17 years receiving a second dose) approached the historical rate of myopericarditis after smallpox vaccination (132.1 cases [81.3–214.6] per million doses) according to Ling and colleagues' study.¹ US military professionals, who are very familiar with adverse events following smallpox vaccination, were among the first to observe myocarditis cases after mRNA COVID-19 vaccines,³ most likely because the US military includes a large number of young men who

received two doses of COVID-19 vaccine very early in the 2021 pandemic vaccine rollout.

Although there are common demographic and clinical features between the myopericarditis cases that followed smallpox vaccine and those that followed mRNA COVID-19 vaccines, better understanding of the pathophysiology of these adverse events following vaccination is an important area for future research. Because smallpox vaccination has very limited global application in the modern era, the experience of mRNA COVID-19 vaccination must now propel the field forward. Analyses of the pathology and immunological mechanisms behind these demographic-dependent adverse events following vaccination are likely to advance our understanding of cardiology and immunology.^{4–6} These advances could spur the development of safer vaccines or precision vaccination practices.⁷

Ling and colleagues' analysis¹ also raises important questions about whether cardiac adverse events following vaccination have historically been well evaluated outside of the realm of smallpox vaccine. In a literature review spanning 75 years, it is remarkable that the study team identified only five publications addressing myocarditis following immunisations other than smallpox or COVID-19 vaccination. The 7 million vaccine doses described in these publications represent a small fraction of the billions of vaccinations administered globally every year.⁸ This challenge might impact the interpretation of the results. Among the populations who received billions of vaccine doses after which myopericarditis was not observed or very rarely observed, published literature might not exist; reassuring data from background populations would not be captured in analyses of the literature, such as those conducted by Ling and colleagues. The safety signal observed after COVID-19 vaccination is, therefore, even more important to fully investigate.⁹

Reports of unexpected adverse events—albeit rare and limited to a specific subset of vaccine recipients—have the potential to damage vaccine confidence at a crucial point in the pandemic response. Like Ling and colleagues, all professionals who have described myopericarditis following COVID-19 vaccination have emphasised

Lancet Respir Med 2022

Published Online

April 11, 2022

[https://doi.org/10.1016/S2213-2600\(22\)00091-1](https://doi.org/10.1016/S2213-2600(22)00091-1)

See Online/Articles

[https://doi.org/10.1016/S2213-2600\(22\)00059-5](https://doi.org/10.1016/S2213-2600(22)00059-5)

that the benefits of vaccination far outweigh the risks during the current pandemic. Nonetheless, scientific knowledge and public health strategies must continue to evolve. Alternative vaccine platforms, vaccine doses, or vaccine schedules could reduce the risk of rare adverse events and must be explored in the context of changing infection risk.¹⁰ Vaccine confidence is one of our most valuable resources, and it is dependent upon trust in public health. Trust is a fragile commodity that is strengthened by reporting challenges transparently and addressing these challenges with scientific rigour and appropriate concern.

We declare no competing interests.

***Margaret Ryan, Jay Montgomery**
m1ryan@ucsd.edu

Immunization Healthcare Division, Defense Health Agency, Falls Church, VA, USA (MR, JM); University of California San Diego, San Diego, CA 92134, USA (MR); Walter Reed National Military Medical Center, Bethesda, MD, USA (JM)

- 1 Ling RR, Ramanathan K, Tan FL, et al. Myopericarditis following COVID-19 vaccination and non-COVID-19 vaccination: a systematic review and meta-analysis. *Lancet Respir Med* 2022; published online April 11. [https://doi.org/10.1016/S2213-2600\(22\)00059-5](https://doi.org/10.1016/S2213-2600(22)00059-5).
- 2 Oster ME, Shay DK, Su JR, et al. Myocarditis cases reported after mRNA-based COVID-19 vaccination in the US from December 2020 to August 2021. *JAMA* 2022; **327**: 331–40.
- 3 Montgomery J, Ryan M, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. *JAMA Cardiol* 2021; **6**: 1202–06.
- 4 Kiblböeck D, Klingel K, Genger M, et al. Myocarditis following mRNA COVID-19 vaccination: call for endomyocardial biopsy. *ESC Heart Fail* 2022; published online Feb 23. <https://doi.org/10.1002/ehf2.13791>.
- 5 Mormile R. Myocarditis and pericarditis following mRNA COVID-19 vaccination in younger patients: is there a shared thread? *Expert Rev Cardiovasc Ther* 2022; **20**: 87–90.
- 6 Hajjo R, Sabbah DA, Bardaweel SK, Tropsha A. Shedding the light on post-vaccine myocarditis and pericarditis in COVID-19 and non-COVID-19 vaccine recipients. *Vaccines (Basel)* 2021; **9**: 1186.
- 7 Kennedy RB, Ovsyannikova IG, Palese P, Poland GA. Current challenges in vaccinology. *Front Immunol* 2020; **11**: 1181.
- 8 Strategic Advisory Group of Experts on Immunization. The Global Vaccine Action Plan 2011–2020. Review and lessons learned (WHO/IVB/19.07). Geneva: World Health Organization, 2019.
- 9 Arnaud M, Bégaud B, Thurin N, Moore N, Pariente A, Salvo F. Methods for safety signal detection in healthcare databases: a literature review. *Expert Opin Drug Saf* 2017; **16**: 721–32.
- 10 Shiri T, Evans M, Talarico CA, et al. The population-wide risk-benefit profile of extending the primary COVID-19 vaccine course compared with an mRNA booster dose program. *Vaccines (Basel)* 2022; **10**: 140.